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(71) Applicant *(for all designated States except US)*: BOEHRINGER MANNHEIM GMBH [DE/DE]; D-68298 Mannheim (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: DI DOMENICO, Roberto [IT/IT]; Viale Monza, 16, I-20127 Milano (IT). DE CILLIS, Gianpiero [IT/IT]; Via S. Pellico, 41, I-20056 Trezzo Sull'Adda (IT). KÖNIG, Bernhard [DE/DE]; Dürrbergstrasse 28, D-82335 Berg (DE). ZIMMERMANN, Gerd [DE/DE]; Domheimer Ring 4, D-68309 Mannheim (DE).

(74) Common Representative: BOEHRINGER MANNHEIM GMBH; Patent Dept., D-68298 Mannheim (DE).

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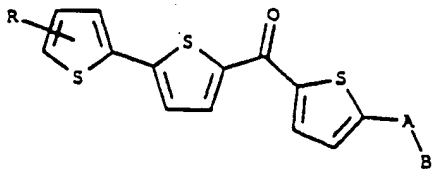
(57) Abstract

Oligo-thiophenes of formula (I) are disclosed wherein: A is a $-CH_2-CO-$, $-CH_2CH_2-CO-$ or $-CH=CH-CO-$ group; B is a 2-thienyl or a phenyl group, which is substituted by an R group, or it is a natural or synthetic amino acid, linked to the A group via its N-terminus; or A-B is a $-CH_2CH_2-NH-A.A.-$ group, wherein the A.A.-group is a natural or synthetic amino acid residue, linked to the CH_2CH_2-NH-group via its carboxy-terminus; R is hydrogen or a chlorine, bromine, iodine, fluorine, (C_1-C_4)alkyle, (C_1-C_4)alkylene- COOR', (C_1-C_4)alkylene-NH_2, (C_1-C_4)alkylene-NR'_2 or (C_1-C_4)alkylene-NHCOR' group; R' is hydrogen or a (C_1-C_4)alkyl group, isomers thereof, and salts thereof with pharmaceutically acceptable acids and bases. It is also claimed the use of the compounds of formula (I) as inhibitors of the uPA binding to the specific uPAR receptor, in particular their application as antitumor and antimetastatic agents.



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OLIGO-THIOPHENES USEFUL AS ANTIMETASTATIC AGENTS, A PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention concerns oligo-thiophenes, optionally linked to natural or synthetic aminoacids.

These compounds have been found to possess uPA-uPAR antagonist activity and can be employed as antitumor and/or antimetastatic agents.

BACKGROUND OF THE INVENTION

The serine proteases uPA (urokinase-type plasminogen activator) catalyzes the activation of plasminogen to plasmin which is involved in a variety of physiological and pathological processes. uPA is a multi-domain protein having a catalytic "B" chain (amino-acids 144-411) and an amino-terminal fragment ("ATF", aa 1-143) comprised of a growth factor-like domain (aa 4-43) and a kringle domain (aa 47-135). uPA is a multifunctional protein involved in tissue proteolysis, cellular migration, cellular proliferation and growth factor activation. uPA is released from cells as a virtually inactive pro-enzyme, pro-uPA. The activation of the single-chain pro-uPA by plasmin (leading to the active two-chain form) is regulated by tight control mechanisms which are not completely understood yet. Most of the uPA activities are confined to the cell surface and the pericellular environment. This is accomplished by binding to a specific, high-affinity receptor on the cell surface (uPAR). Both forms of uPA bind to uPAR with similar affinity. The binding interaction is mediated by the growth factor-like domain [S.A. Rabbani et al., *J. Biol. Chem.*, 267, 14151-56, 1992].

The uPA receptor is a three domain glycoprotein where each triplicated motif comprizes a cysteine rich consensus sequence of approximately 90 amino acids [M. Plough et al., *J. Biol. Chem.*, 268, 17539-46, 1993]. uPAR is anchored to cell membrane by a glycosyl-phosphatidylinositol moiety (GPI anchor). uPAR binds uPA with K_D values between 10^{-10} and 10^{-9} M, depending on the experimental system. The major determinants for uPA binding are located in the N-terminal domain 1. uPAR can be cleaved by uPA and plasmin, liberating a water soluble domain 1 and by the action of phospholipase C, three domains uPAR (1+2+3) can be released from the cell surface. This latter form of uPAR is also water soluble because the GPI-anchor is missing.

The inhibition of uPA dependent phenomena can principally be approached in two ways, either by direct inhibition of the proteolytic activity or by inhibition of uPA receptor

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binding. The latter strategy has the potential of achieving greater specificity since inhibition might be localized to the pericellular environment.

A bacteriophage display technique and protein engineering have recently been used to discover peptidic and species-specific uPAR antagonists [Goodson et al., *PNAS*, 91, 7129, 1994; Stratton-Thomas et al., *Prot. Eng.*, 5, 463-470, 1995, respectively].

The present invention concerns oligo-thiophenes with potent antagonistic activity.

Many bisthiophene and terthiophene derivatives seem to display interesting biological properties [Kagan, J. et al., *J. Org. Chem.*, 48, 4317-20, 1983 and references cited therein]. Most notably they are toxic to nematodes and this effect can be greatly enhanced by the presence of ultraviolet light. The most carefully scrutinized of these compounds is α-terthienyl, a plant-derived natural product first recognized as phototoxin in the 1970s. This compound showed photoenhanced activity against nematodes, microorganisms, algae, human erythrocytes, insect larvae and eggs, in addition to generating skin pigmentation, acting as herbicide and as a seed germination inhibitor. Photoactive antiviral and cytotoxic activities were also reported [(a) Cooper et al., *Bioorg. Chem.*, 13, 362-374, 1985 and references cited therein; (b) Rawls et al., *Chem. & Engin. News*, 21-23, 1986; (c) Evans et al., *J. Am. Chem. Soc.*, 112, 2694-2701, 1990; (d) Kyo et al., *Plant Cell Rep.*, 9, 393-397, 1990; (e) Hudson et al., *Planta Med.*, 59, 447-450, 1993; (f) Hudson et al., *Chemosphere*, 19, 1329-1343, 1989]. A structure-activity relationship study was announced for the fourteen isomeric unsubstituted terthiophenes [Jayasuriya et al., *Heterocycles*, 24, 2261-2264 and 2901-2904, 1986].

The use of the thiophene ring is largely widespread in the different fields of therapeutic agents, while oligothiophenes are only rarely mentioned as pharmacological agents [Press et al., *The Chemistry of Heterocycles Compounds*, vol. 44, part four, chapter III, edited by Salo Gronowitz, 396-502, 1989].

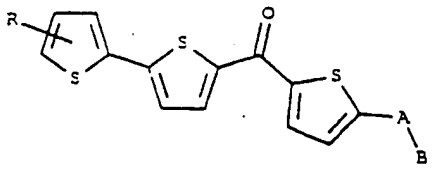
The uPA/uPAR system has been shown to be implicated in a variety of invasive biological processes such as tumor metastasis, trophoblast implantation, inflammation and angiogenesis. Therefore, uPAR antagonists should be able to block tumor invasiveness, metastasis and angiogenesis. Formulations containing uPAR antagonists represent novel therapeutic treatments for a number of highly invasive and metastazising cancers where uPA and uPAR have been found to be consistently present at the invasive foci of the tumor [Dano et al., *Proteolysis and Protein Turnover*, eds. Barret + Bond, Portlan Press, 1994, London] (e.g. breast, lung, colon, ovarian cancers). In patients with

breast cancer and non-small cell lung cancer increased levels of uPAR in plasma have been detected. Therefore, the amount of soluble uPAR appears to reflect the degree of proteolysis in the tumor and this might be closely related to patient prognosis. Both uPA and uPAR levels in tumor tissue are prognostic factors in may types of cancers.

In addition to cancer, other diseases mediated by cell-surface activity of uPA are addressed by uPAR antagonists. Inhibitors of plasmin generation by receptor bound uPA therefore have mechanism-based tumoristatic, anti-invasive, anti-metastatic, anti-angiogenic, anti-arthritic, anti-inflammatory, anti-osteoporotic, anti-retinopathic and contraceptive activities. These compounds are applied preferentially via the oral route, but also by i.v. or i.m. injections, nasal sprays or any other conventionally used application.

DESCRIPTION OF THE INVENTION

The present invention concerns oligo-thiophenes of the general formula (I):



(I)

wherein:

- A is a $-CH_2-CO-$, $-CH_2CH_2-CO-$ or $-CH=CH-CO-$ group;
- B is a 2-thienyl or a phenyl group, which is substituted by an R group, or it is a natural or synthetic amino acid, linked to the A group via its N-terminus; or A-B is a $-CH_2CH_2-NH-A.A.-$group, wherein the A.A.-group is a natural or synthetic amino acid residue, linked to the CH_2CH_2-NH-group via its carboxy-terminus;
- R is hydrogen or a chlorine, bromine, iodine, fluorine, (C_1-C_4)alkyl, (C_1-C_4)alkylene- COOR', (C_1-C_4)alkylene-NH_2, (C_1-C_4)alkylene-NR'_2 or (C_1-C_4)alkylene-NHCOR' group;
- R' is hydrogen or a (C_1-C_4)alkyl group,

isomers thereof, and salts thereof with pharmaceutically acceptable acids and bases.

A natural amino acid denotes one of the 20 α-amino acids which are the monomer units for polypeptides, for example Glycine, alanine, valine, leucine isoleucine, phenylalanine, tryptophan, proline, serine, threonine, tyrosine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, arginine, histidine, cysteine or methionine.

A synthetic amino acid consists of a compound comprising an amino group together with a carboxy group linked to the α-carbon atom.

Pharmaceutically acceptable salts of compounds of the present invention include physiologically acceptable acid addition salts for example hydrochlorides, hydrobromides, sulphates, methane sulphonates, p-toluensulphonates, phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates. Salts may also be formed with bases, for example sodium, potassium, magnesium, and calcium salts.

Preferred compounds are those in which B is an amino acid or A-B is a group of formula $-CH_2CH_2-NH-A.A.$

Other preferred compounds are those in which B is a 2-thienyl group.

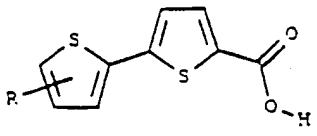
Particularly preferred compounds are those in which the aminoacid is triptophane.

Another object of the present invention is to provide a process for the preparation of the compounds of formula (I).

A further object of the present invention is the use of the compounds of formula (I) for the treatment of the diseases in which an inhibitor of the uPAR can be effective, in particular tumor and tumor metastasis or invaisveness, as well as pharmaceutical compositions containing a pharmacologically effective amount of one or more compounds of formula (I) in admixture with pharmaceutically suitable additives.

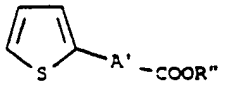
PREPARATION OF THE COMPOUNDS OF THE INVENTION

The compounds of formula (I) in which B is a natural or synthetic amino acid (hereinafter referred to as -A.A.-) can be prepared starting from the intermediate of formula (II):



(II)

which is first transformed into the corresponding acyl chloride derivative and then it is reacted via Friedel-Craft reaction with the intermediate of formula (III):



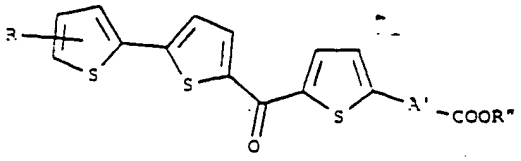
(III)

wherein A' is a $-CH_2-$, $-CH_2CH_2-$ or -CH=CH- group and R" is a (C_1-C_4)alkyl group, in the presence of a Lewis acid.

The transformation of the intermediate (II) into its acyl chloride is preferentially performed with thionyl chloride, which is used also as the solvent, at temperature between room temperature and the boiling temperature of the solvent.

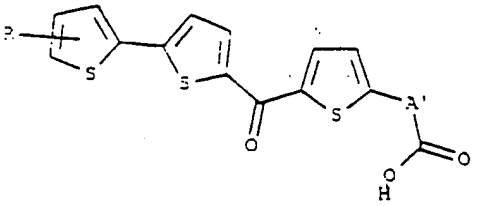
The Friedel-Craft reaction is performed in an inert solvent and at a temperature ranging from -5°C and room temperature, using preferentially $SnCl_4$ as the Lewis acid.

The intermediate (IV) so obtained:



(IV)

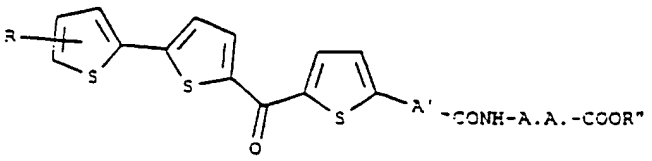
is hydrolized into the corresponding acid of formula (V):



(V)

Suitable reaction conditions comprise the use of a base, preferentially an alkaline metal hydroxide, in water, an alcohol or mixtures thereof, at a temperature ranging from 0°C to room temperature.

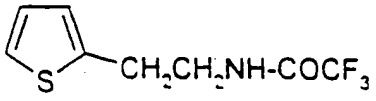
The carboxylic group of intermediate (V) is then activated, for example with carbonyldiimidazole to give the imidazolyl derivative, and subsequently reacted, preferentially in an inert solvent and at a temperature between 0°C and 50°C, with an amino acid of formula -A.A.-, to give the intermediates of formula (VI):



(VI)

which are then converted into the corresponding compounds of formula (I) via hydrolysis of the carboxylic ester -COOR", preferentially in acidic conditions.

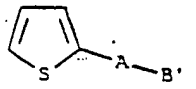
If in the above process the intermediate of formula (III) is replaced by an intermediate of formula (III'):



(III')

the compounds of formula (I) in which A-B is a -CH_2CH_2-NH-A.A.-group can be prepared. In this case, the -$COCF_3$ protecting group should be removed after the Friedel-Craft reaction and the intermediate so obtained should be condensed with a N-BOC-amino acid, previously activated through its carboxyl group. The compounds of formula (I) are finally obtained after removal of the BOC protecting group.

The compounds of formula (I) in which B is a 2-thienyl or a phenyl group, which is substituted by an R group having the above meanings, can be prepared by Friedel-Craft reaction of the intermediate of formula (II), activated in its carboxylic functionality as described above, with an intermediate of formula (VII):

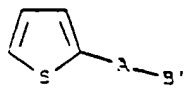


(VII)

wherein A has the meanings shown above and B' is a 2-thienyl or a phenyl group, which is substituted by an R group as shown above.

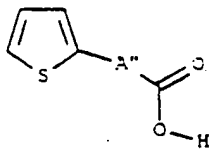
The intermediates of formula (II) can be obtained by reaction of a bis-thiophene, substituted on one ring with the R substituents, with carbon dioxide and a strong base such as butyl lithium, at a temperature between -50°C and -20°C. The starting products bis-thiophenes are commercially available or can be prepared according to procedures well known to one skilled in the art.

The intermediates of formula (VII):



(VII)

wherein A is -CH_2-CO- or -CH=CH-CO- can be obtained starting from the commercially available intermediates of formula (VIII):



(VIII)

wherein A" is -CH_2- or -CH=CH-, via transformation of the carboxylic functionality into its corresponding acyl chloride and subsequent Friedel-Craft reaction with a compound of formula B-H, wherein B-H is a thiophene or phenyl group substituted with an R group as shown above.

The intermediates of formula (VII) in which A is -CH_2CH_2-CO- can be obtained from the corresponding intermediates with A = -CH=CH-CO- via hydrogenation of the C=C double bond in the presence of a suitable catalyst, such as $(PPh_3)_3RhCl$.

Analogously, the intermediates of formula (III) in which A' is $-CH_2CH_2-$ can be obtained from the corresponding C=C carrying intermediates via catalytic hydrogenation.

BIOLOGICAL ACTIVITY

The compounds of the invention were tested (ELISA test) as inhibitors of human urokinase (uPA) binding to its specific receptor uPAR mAk (BIO-R4), according to the procedure described in Biol. Chem. Hoppe-Seyler, 376, 587-94 (1995) by Rettenberger et al..

The assays are performed in Microtiterplates (96 wells). The following solutions are used:

- washing buffer: PBS-buffer (without Mg^{2+} and Ca^{2+}) + 0.05% Tween 20;
- incubation buffer (IP): 1% skimmed milk powder in PBS-buffer (without Mg^{2+} and Ca^{2+});
- BIO-R4 solution: 50 ng/well (0.5 Tg/ml; 100 Tl/well) in IP;
- uPAR solution: 3 ng/well (30 ng/ml; 100 Tl/well) in PBS-buffer (without Mg^{2+} and Ca^{2+});
- blocking solution: 1% skimmed milk powder in washing buffer (dissolved at 37°C);
- uPA solution: 0.25 ng/well (5 ng/ml; 50 Tl/well) in IP.

Detection solutions (per microtiterplate):

(1) 6 ml (100 mM Tris-Cl pH 7.2 + 0.15% Tween 80) + 1.5 ml (10 Tg) Plasminogen in aqua bidest;

(2) 6 ml (100 mM Tris-Cl pH 7.2 + 0.15% Tween 80) + 1.5 ml (7.5 mg) chromozyme PL in aqua bidest.

The detection solution must be continously stirred.

Testing substances: the testing substances are dissolved in DMSO. They are used in the test system with a highest concentration of 100 Tg/ml. The solutions are prepared using PBS.

Three controls are performed:

a) positive control: using 2% DMSO in PBS;

b) negative control: assay without receptor;

c) inhibition control: 1) inhibition (IC_{95} at 0.25 mg/ml) with dextranesulfate (MW = 500.000);

2) inhibition (IC_{90} at 1 Tg/ml) with inactivated uPA (175 Tg/ml).

Incubation is done as follows:

Each well is incubated by 100 Tl of BIO-R4 (c=0.5 Tg/ml) for 1 hour at room temperature under shaking. After washing three times with the washing buffer, each well is incubated for 1 hour (37°C) with 200 Tl/well blocking solution. After triple washing each well is incubated for 1 hour at room temperature under shaking with 100 Tl/well uPAR (c=30 ng/ml), then the wells are washed again three times with the washing buffer. The testing substance solution and the control solution, respectively, are added (50 Tl/well) and are incubated for 30 minutes at room temperature under shaking. An additional 50 Tl of uPA solution (c=2.5 ng/ml) are added. After 1 hour at room temperature a triple washing is performed.

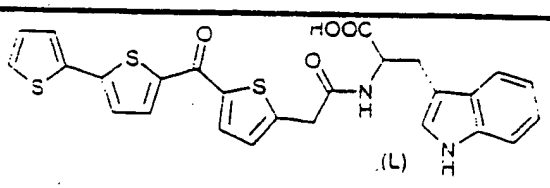
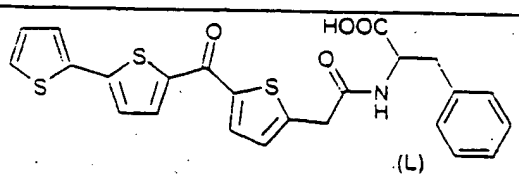
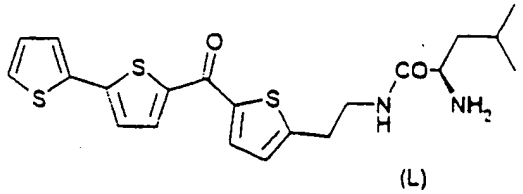
For detection, the following procedure is used:

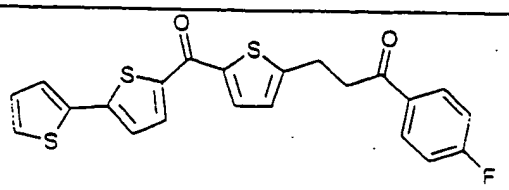
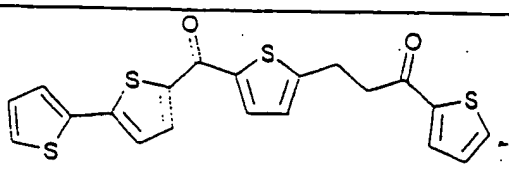
Incubation with 50 Tl each of detection solution (1) and (2) at room temperature. After 20 minutes a yellow colour will be risible (the positive control reads an extinction of 1 after 45-60 minutes). The detection is performed at 405 nm (reference is 490 nm) using a Dynatech MR 7000 ELISA reader. To obtain the percentage of inhibition the following formula is used (E stands for extinction):

$$\% \text{ Inhibition} = 100 - 100 \times [E_{test} - E_{neg.\ control} / E_{pos.\ control} - E_{neg.\ control}]$$

The data for some representative compounds of the invention are reported in table I.

Table I - BIO-R4 Assay - Inhibition of uPA binding to the specific uPAR receptor (BIO-R4) expressed as IC_{50} (mM)

structure	example	IC_{50} (mM)
	2	0.0057
	6, cpd. 3	0.0058
	9, cpd. 1	0.002

	5	1.9
	3	0.7

The invention concerns pharmaceutical agents containing one or more compounds of formula (I).

In order to produce pharmaceutical agents, the compounds of formula (I) are mixed in a known manner with suitable pharmaceutical carrier substances, aromatics, flavouring and dyes and are formed for example into tablets or coated tablets or they are suspended or dissolved in water or an oil such as e.g. olive oil with addition of appropriate auxiliary substances.

The substance of the general formula (I) can be administered orally or parenterally in a liquid or solid form. Water is preferably used as the medium which contains the stabilizing agents, solubilizers and/or buffers which are usually used for injection solutions. Such additives are for example tartrate or borate buffers, ethanol, dimethylsulfoxide, complexing agents (such as ethylendiaminotetraacetic acid), high molucular polymers (such as liquid polyethylene oxide) for the regulation of the viscosity or polyethylene derivatives of sorbitol anhydrides.

Solid carrier substances are e.g. starch , lactose, mannitol, methylcellulose, talcum, highly dispersed silicic acid, higher molecular fatty acids (such as stearic acid), gelatin, agar-agar, calcium phosphate, magnesium stearate, animal and vegetable fats or solid high molecular polymers (such as polyethylene glycols). Suitable formulations for the oral route can if desired contain flavourings and sweeteners.

The administered dose depends on the age, the health and the weight of the patient, the extent of the disease, the type of treatments which are possibly being carried out concurrently, the frequency of the treatment and the type of the desired effect. The daily dose of the active compound is usually 0.1 to 50 mg/kg body weight. Normally 0.5 to 40 and preferably 1 to 20 mg/kg/day in one or several applications per day are effective in order to obtain the desired results.

The invention is further illustrated by the following examples.

Preparation 1 - Synthesis of bis-thiophene-2-carboxylic acid

15 g of bis-thiophene are dissolved in 300 ml of tetrahydrofuran (THF) and the solution is cooled at -40°C under a nitrogen atmosphere. 10.8 ml of 10 M buthyl lithium in hexane are cautiously dropped, then the red solution is kept at -10°C for 1 hour and it is poured into a flask containing 500 g of dry ice (solid carbon dioxide). The yellow suspension dissolves in 1 hour, then the resulting solution is poured into 1000 ml of 2 N sodium hydroxide. After 30 minutes the organic phase is separated off and the solvent is concentrated to a little volume. The residue is added with 2 N sodium hydroxide and water and washed with hexane, then the aqueous phase is acidified to pH = 2 with 37% hydrochloric acid, kept for 1 hour at room temperature, and the solid is filtered and washed with 50 ml of water. After drying it in an oven at 70°C, 17.8 g of the product are obtained, m.p. 171-174°C

Preparation 2 - Synthesis of 2-[3-(2-thienyl)acryloyl]thiophene

A solution of 5 g of 3-(2-thienyl)acrylic acid in 30 ml of thionyl chloride is heated at 50°C for 1 hour 30 minutes, then the unreacted thionyl chloride is eliminated under reduced pressure. The residue is added with 20 ml of heptane and dried twice, then it is dissolved in 50 ml of methylene chloride, cooled at 0°C and added dropwise with a solution of 2.43 g of thiophene in 5 ml of methylene chloride. Keeping the temperature at 0°C, a solution of 6.74 ml of $SnCl_4$ in 12 ml of methylene chloride is then dropped. The reaction mixture is kept at room temperature for 2 hours, then it is poured into 200 ml of 2 N hydrochloric acid. The aqueous phase is separated and extracted with 100 ml of methylene chloride. The organic phase is dried over sodium sulfate and evaporated to dryness and the residue is purified by silica gel chromatography (eluent hexane/ethyl acetate 5:1), obtaining, after recrystallization from hexane, 4.79 g of the product, m.p. 105-107°C.

Preparation 3 - Synthesis of 2-[3-(2-thienyl)propanoyl]thiophene

A solution of 4.64 g of 2-[3-(2-thienyl)acryloyl]thiophene in 50 ml of dry methylene chloride and 0.97 g of tris(triphenylphosphine)rhodium chloride is hydrogenated at room temperature overnight. The reaction mixture is then concentrated to dryness and purified by silica gel chromatography (eluent hexane/ethyl acetate 20:1) to give 4.3 g of the product as an oil.

Preparation 4 - Synthesis of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetic acid, ethyl ester

A solution of bis-thiophene-2-carboxylic acid (3 g; preparation 1) in 20 ml of thionyl chloride is heated at 50°C for 1 hour 30 minutes, then the unreacted thionyl chloride is evaporated off and the residue is treated three times with 10 ml of heptane and evaporated. The residue is dissolved in methylene chloride and cooled at 0°C, then it is added dropwise with a solution of 2-(thien-2-yl)acetic acid, ethyl ester (2.19 g) in 5 ml of methylene chloride. A solution of $SnCl_4$ (3 ml) in 10 ml of methylene chloride is subsequently added. The reaction mixture is kept at room temperature for 2 hours, then it is poured into 200 ml of 2 N hydrochloric acid. The aqueous phase is extracted with methylene chloride (3x150 ml) and the organic extracts are collected, dried over sodium sulfate and concentrated to dryness. The residue (8 g) is purified by silica gel chromatography (eluent hexane/ethyl acetate 8:1) to give 3.62 of the product.

Preparation 5 - Synthesis of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetic acid

A suspension of 3.62 g of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetic acid, ethyl ester, in 60 ml of ethanol and 5 ml of water is cooled at 0°C and added with 11.35 ml of 2 N sodium hydroxide. The mixture is kept at room temperature overnight, then it is concentrated to a little volume. After acidification, the product crystallizes, which is then separated by filtration and dried under vacuum at 40°C. 2.4 g of the product are recovered.

Preparation 6 - 4-[3-(2-thienyl)propanoyl]-1-fluorobenzene

5 g of 2-(2-thienylidene)-4-fluoroacetophenone are dissolved in 50 ml of dry methylene chloride and added with 0.97 g of tris(triphenylphosphine)rhodium chloride. The reaction is hydrogenated for 8 hours (about 470 ml of hydrogen are reacted), then it is concentrated to dryness and purified by silica gel chromatography (eluant hexane/ethyl acetate 20 : 1), to give 4.85 g of the product.

Preparation 7 - 2-[2-(trifluoroacetamido)-1-ethyl]thiophene

A solution of 2-(2-thienyl)ethylamine (10 g) in 100 ml of tetrahydrofuran is cooled to 0°C then it is added dropwise with 9.05 ml of ethyl trifluoroacetate. After 4 hours under stirring at room temperature the reaction mixture is concentrated to dryness to give 18 g of an oil which is treated with 18 ml of ethyl ether and saturated with 90 ml of hexane. After cooling for 2 hours 12.15 g of the product are collected by filtration, m.p. 45-47°C.

Preparation 8 - 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]-N-trifluoroacetylethylamine

A solution of bis-thiophene-2-carboxylic acid (3.4 g; preparation 1) in 25 ml of thionyl chloride is heated at 50°C for 2 hours. The reaction mixture is concentrated to dryness, then it is redissolved in heptane and concentrated again to dryness. This work up is repeated, then the residue is dissolved in methylene chloride, cooled at 0°C and added dropwise with a solution of 3.3 g of 2-[2-(trifluoroacetamido)-1-ethyl]thiophene (preparation 7) in 20 ml of methylene chloride and subsequently with a solution of $SnCl_4$ (3.8 ml) in 3.8 ml of methylene chloride. The reaction mixture is kept under stirring at room temperature for 2 hours, then it is poured into 200 ml of 2 N hydrochloric acid and extracted with tetrahydrofuran (4 x 100 ml). The organic extracts are pooled, dried over sodium sulfate and the solvent is evaporated under reduced pressure. 18 g of a black oil are obtained, which is purified by silica gel chromatography (eluant hexane/tetrahydrofuran 2 : 1). After recrystallization from hexane (100 ml) and drying under vacuum at 50°C, 4.3 g of the product are obtained, m.p. 168-170°C.

Preparation 9 -2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamine

To a mixture of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]-N-trifluoroacetylethylamine (10 g; preparation 8) in 800 ml of methanol, cooled at 0°C and kept under stirring, 60.17 ml of 2 N sodium hydroxide are added and the reaction mixture is heated at 50°C overnight. The mixture is then concentrated to a little volume, then it is added with water (500 ml) and extracted with chloroform (4 x 200 ml). The organic extracts are pooled, dried over sodium sulfate and concentrated to dryness. After crystallization from a ethyl acetate (16 ml)/hexane (16 ml) mixture, 5.1 g of the product are obtained, m.p. 102-104°C.

Example 1 - Synthesis of N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]triptophane, ethyl ester

A suspension of 2.34 g of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetic acid (preparation 5) and 1.74 g of carbonyldiimidazole in 150 ml of dry THF is kept at 40°C for 1 hour. The mixture is cooled to 20°C and it is added dropwise with a solution of 2.45 g of triptophane ethyl ester in 10 ml of dry THF. After 2 hours the reaction mixture is concentrated to dryness, then it is dissolved in ethyl acetate, washed with water and extracted with 200 ml of chloroform. The organic phase is concentrated to dryness to

give 7 g of a residue which is purified by silica gel chromatography (eluent hexane/ethyl acetate from 4:1 to 2:1). 2.79 g of the product are obtained.

Example 2 - Synthesis of N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]triptophane

A solution of 2.2 g of N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]triptophane, ethyl ester (example 1) in 320 ml of ethanol and 10 ml of water is cooled at 0°C, then it is added dropwise with 4.43 ml of 2 N sodium hydroxide. After 4 hours at room temperature, the mixture is concentrated to a little volume, added with water, washed with ethyl acetate and acidified to pH = 2. The aqueous phase is extracted with ethyl acetate, the organic extracts is dried over sodium sulfate, concentrated to dryness and the residue is purified by silica gel chromatography (eluent chloroform/methanol/acetic acid 9:1:0.25) to give 1.16 g of the product, m.p. 166-168°C.

Example 3 - Synthesis of 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]thiophene

A solution of 1 g of bis-thiophene-2-carboxylic acid (preparation 1) in 5 ml of thionyl chloride is heated at 50°C for 1 hour 30 minutes, then the unreacted thionyl chloride is evaporated off and the residue is added with heptane and again evaporated. The residue is dissolved in methylene chloride, cooled at 0°C and added dropwise with a solution of 2-[3-(2-thienyl)propanoyl]thiophene (1 g; preparation 3) in 3 ml of dry methylene chloride. A solution of 1.05 ml of $SnCl_4$ in 3 ml of dry methylene chloride is then dropped, keeping the temperature at 0°C. The reaction mixture is kept at room temperature for 1 hour, then it is poured into 100 ml of 2 N hydrochloric acid, extracted with ethyl acetate (3x100 ml), dried over sodium sulfate and concentrated to dryness. The residue (3 g) is purified by silica gel chromatography (eluent hexane/ethyl acetate 5:1) to give 1.02 g of the product, m.p. 124-126°C.

Example 4 - Synthesis of 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]thiophene

A solution of 0.24 g of bis-thiophene-2-carboxylic acid (preparation 1) in 3 ml of thionyl chloride is heated at 50°C for 1 hour 30 minutes, then the unreacted thionyl chloride is evaporated off and the residue is added with heptane and again evaporated. The residue is dissolved in methylene chloride, cooled at 0°C and added dropwise with a solution of 2-[3-(2-thienyl)acryloyl]thiophene (0.3 g; preparation 2) in 3 ml of dry methylene

chloride. A solution of 0.31 ml of $SnCl_4$ in 3 ml of dry methylene chloride is then dropped, keeping the temperature at 0°C. The reaction mixture is kept at room temperature for 4 hour, then further 0.3 ml of $SnCl_4$ are added and the mixture is kept at room temperature overnight. The reaction mixture is poured into 200 ml of 2 N hydrochloric acid, extracted with ethyl acetate (3x50 ml), dried over sodium sulfate and concentrated to dryness. The residue (1.3 g) is purified by silica gel chromatography (eluent hexane/ethyl acetate 5:1, then pure ethyl acetate) to give 0.37 g of the product.

Example 5 - Synthesis of 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-fluorobenzene

1.06 g of bis-thiophene-2-carboxylic acid (preparation 1) in 10 ml of thionyl chloride are heated at 50°C for 1 hour 30 minutes, then the mixture is concentrated to dryness. The residue is treated twice with 20 ml of heptane, finally with 30 ml of methylene chloride, cooled to 0°C and added dropwise with a solution of 4-[3-(2-thienyl)propanoyl]-1-fluorobenzene (1.08 g; preparation 6) in 5 ml of methylene chloride. Keeping the temperature at about 0°C, a solution of $SnCl_4$ (1.07 ml) in 5 ml of methylene chloride is added dropwise, then the mixture is stirred at room temperature for 2 hours. The reaction mixture is poured into 150 ml of 2 N hydrochloric acid, then it is extracted with ethyl acetate and the organic phase is concentrated to dryness. The residue is purified by silica gel chromatography (eluant methylene chloride), to give, after crystallization from ethyl acetate/hexane mixture, 1 g of the product, m.p. 138-140°C.

Example 6 -

According to the procedures described in the previous preparations and examples, the following oligothiophene derivatives are obtained:

- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]glycine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]alanine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]phenylalanine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]tyrosine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]leucine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]lysine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]serine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]isoleucine;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-fluorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-chlorobenzene;

- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-2-bromobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-(carboxymethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-(aminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-3-(dimethylaminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-2-(tert-butyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-fluorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-chlorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-2-bromobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-(carboxymethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-(aminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-3-(dimethylaminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-2-(tert-butyl)benzene.

Example 7 - 4-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylaminocarbonyl]-2-(tert-butoxycarbonylamino)butanoic acid

A mixture of glutammic acid N-BOC (0.88 g) and 1,1'-carbonyldiimidazole (0.63 g) in 40 ml of tetrahydrofuran is kept under stirring at room temperature for 2 hours, then a solution of 2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamine (1.11 g; preparation 9) in 40 ml of tetrahydrofuran is added dropwise and the reaction mixture is heated at 50°C overnight. The solvent is evaporated under reduced pressure and the residue is dissolved in ethyl acetate and washed with a saturated aqueous solution of potassium hydrogensulfate. After separation by filtration of the solid which separates (starting product), the organic phase is concentrated to dryness. The residue (2.5 g) is purified by silica gel chromatography (eluant 1) chloroform/methanol 15 : 2; 2) chloroform/methanol 9 : 1), to give 0.42 g of the product.

Example 8 - 4-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylaminocarbonyl]-2-aminobutanoic acid

A suspension of 4-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylaminocarbonyl]-2-(tert-butoxycarbonylamino)butanoic acid (0.28 g; example 7) in 28 ml of methylene chloride is added with 0.39 ml of trifluoroacetic acid. The resulting dark solution is kept under stirring at room temperature overnight, then it is concentrated to dryness. The residue is redissolved in absolute ethanol (15 ml), then it is concentrated again to

dryness and this work up is repeated another time. The residue (0.3 g) is suspended in 20 ml of hexane, stirred for 1 hour at room temperature, filtered and dried under vacuum at 30°C. 0.2 g of the product are obtained.

^{1}H-NMR in d6-DMSO + D_2O: 1.9 ppm (m, 2H); 2.18 ppm (m, 2H); 3.05 ppm (m, 2H); 3.36 ppm (br m, 2H); 3.7 ppm (t, 1H); 7.1 ppm (m, 2H); 7.5 ppm (m, 3H); 7.9 ppm (m, 2H); 8.61 ppm (br t, 1H).

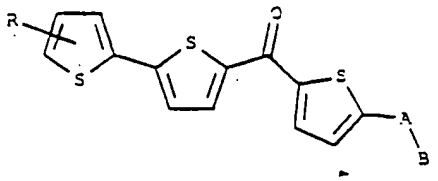
Example 9 -

According to the methods described in examples 7 and 8, starting from the suitable amino acids, the following oligo-thiophenes are obtained:

- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]leucinamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]phenylalaninamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]serinamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]lysinamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]isoleucinamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]istidinamide;
- [2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]ethylamino]tyrosinamide.

CLAIMS

1. Oligo-thiophenes of the general formula (I):



(I)

wherein:

- A is a $-CH_2-CO-$, $-CH_2CH_2-CO-$ or $-CH=CH-CO-$ group;
- B is a 2-thienyl or a phenyl group, which is substituted by an R group, or it is a natural or synthetic amino acid, linked to the A group via its N-terminus; or A-B is a $-CH_2CH_2-NH-A.A.-$group, wherein the A.A.-group is a natural or synthetic amino acid residue, linked to the CH_2CH_2-NH-group via its carboxy-terminus;
- R is hydrogen or a chlorine, bromine, iodine, fluorine, (C_1-C_4)alkyl, (C_1-C_4)alkylene- COOR', (C_1-C_4)alkylene-NH_2, (C_1-C_4)alkylene-NR'_2 or (C_1-C_4)alkylene-NHCOR' group;
- R' is hydrogen or a (C_1-C_4)alkyl group,

isomers thereof, and salts thereof with pharmaceutically acceptable acids and bases.

2. Oligo-thiophenes according to claim 1, wherein B is an amino acid.

3. Oligo-thiophenes according to claim 2, wherein A-B is a group of formula $-CH_2CH_2-NH-A.A.-$.

4. Oligo-thiophenes according to claims 1 to 3, wherein the amino acid is triptophane.

5. Oligo-thiophenes according to claim 1, wherein B is a 2-thienyl group.

6. Oligo-thiophenes according to claim 1, selected from:

- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]triptophane;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]thiophene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]thiophene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-fluorobenzene;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]glycine;

- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]alanine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]phenylalanine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]tyrosine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]leucine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]lysine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]serine;
- N-[2-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acetyl]isoleucine;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-fluorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-chlorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-2-bromobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-(carboxymethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-4-(aminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-3-(dimethylaminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]propanoyl]-2-(tert-butyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-fluorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-chlorobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-2-bromobenzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-(carboxymethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-4-(aminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-3-(dimethylaminomethyl)benzene;
- 2-[3-[2-((2,2'-bisthien-5'-yl)carbonyl)thien-5-yl]acryloyl]-2-(tert-butyl)benzene.

7. Pharmaceutical compositions containing a pharmacologically effective amount of one or more compounds of claims 1 to 6 in admixture with pharmaceutically acceptable eccipients.

8. The use of compounds of claims 1 to 6 for the preparation of a medicament having antitumor and antimetastatic activity.

9. Compounds of claims 1 to 6 for use as inhibitors of uPA binding to the specific uPAR receptor.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/04705

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D333/24 C07D409/14 A61K31/38 A61K31/405

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 32190 A (XENOVA LTD ;BRYANS JUSTIN STEPHEN (GB); FOLKES ADRIAN JOHN (GB); L) 30 November 1995 see abstract; claim 1 ---	1-9
A	E. LESCOT ET AL.: "Thiophen Derivatives. Part XIV. Some Problems of Substitution in the 2,2'-Bithienyl Series" JOURNAL OF THE CHEMICAL SOCIETY,1959, pages 3234-3237, XP002051010 LONDON see page 3236 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1998	10/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 98/04705

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